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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/932,521	08/17/2001	Hans Herweijer	Mirus.023.01	4294

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EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	PAPER NUMBER
1632	
MAIL DATE	DELIVERY MODE
10/30/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/932,521	HERWEIJER ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15 and 17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. In view of the Appeal brief filed on 08/14/2008, PROSECUTION IS HEREBY REOPENED. New grounds of rejections are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

/Peter Paras, Jr./
Supervisory Patent Examiner, Art Unit 1632.

The examiner prosecuting this case has changed. All inquiries directed to the application should be directed to examiner W. - C. Winston Shen.

This application 09/932,521filed on 08/17/2001 claims benefit of 60/225,946 filed on 08/17/2000.

Claims 1-15 and 17 are currently under examination.

Previous rejection of claims 1-15 and 17 (page 4-5 of office action mailed on 10/06/2005) under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because the claims are vague and appear to be incomplete because there is no embodiment within the claims that requires the expression, is *withdrawn* upon further consideration.

Previous rejection of claims 1-15 and 17 (pages 2-4 of office action mailed on 10/06/2005) under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed had possession of the claimed invention, is *withdrawn* upon further consideration.

Previous rejection of claims 1-15 and 17 (page 3 of office action mailed on 10/06/2005) under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described, is *withdrawn* upon further consideration.

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1, 3, 5, 7, 8, 10, and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Yant et al.** (Yant et al., Somatic integration and long-term transgene expression in normal and haemophilic mice using a DNA transposon system, *Nat Genet.* 25(1):35-41, 2000) in view of **Neumann et al.** (Neumann et al., Gene transfer into mouse lyoma cells by electroporation in high electric fields, *EMBO J.* 1(7):841-5, 1982).

Claim 1 amended on 07/07/2005 reads as follows: A process for in *vivo* expression of longer than seven days of a non-viral linear DNA nucleic acid sequence from a delivered expression cassette, comprising: a) providing the expression cassette comprising the nucleic acid sequence operably linked to a promoter; b) forming a non-viral, linearized plasmid DNA vector comprising the expression cassette; and, c) delivering the non-viral, linearized plasmid DNA vector to a hepatocyte in a mammal, wherein providing the expression cassette on the non-viral, linearized plasmid DNA vector results in increased expression in the hepatocyte after seven days defined by at least 20% more gone product than is expressed from a supercoiled plasmid from which the linearized plasmid is derived.

Claim interpretation: The limitation "delivering the non-viral, linearized plasmid DNA vector to a hepatocyte in a mammal" reads on direct and indirect delivery of the non-viral, linearized plasmid DNA vector to a hepatocyte in a mammal. For direct delivery to a hepatocyte, claim 1 as written reads transfection of hepatocyte *in vitro* followed by transplantation of transfected hepatocyte in a mammal. For indirect delivery to a hepatocyte, any route of administration of the DNA will result in the presence of DNA in the liver cells because liver is a major organ for metabolism.

Yant et al. teaches the development of non-viral gene-transfer technologies that can support stable chromosomal integration and persistent gene expression *in vivo* is desirable. Yant et al. describes the successful use of transposon technology for mouse hepatocyte transfection *in vivo* by the nonhomologous insertion of foreign genes into the genomes of adult mammals using naked plasmid DNA , pTori, pCMC-SB and pCMV-mSB (See left column, page 36, and Figures 1 and 3, Yant et al.,. 2000). The plasmids taught by Yant et al. comprise Tn5 transposase recognition elements (See Figure 2b and 2d, Yant et al., 2000). Yant et al. shows that chromosomal transposition resulted in long-term expression (>5 months) of human blood coagulation factor IX at levels that were therapeutic in a mouse model of haemophilia B (See Table 1 and Figure 4, Yant et al. 2000). The results demonstrated by Yant et al. establishes DNA-mediated transposition as a new genetic tool for mammals, and provide new strategies to improve existing non-viral plasmid vectors for human gene therapy applications (See abstract, Yant et al., 2000).

However, Yant et al. does not teach using linearized DNA vector for mammalian transfection.

Neumann et al. investigated transfecting mouse cells in the presence of electric impulses and reported that linearized plasmid DNA molecules work several folds better than circular/supercoiled DNA molecules to obtain stable transformed mouse cells based on the selection of herpes simplex thymidine kinase (TK) reporter gene (See abstract and Figure 3, Neumann et al., 1982) cloned in a recombinant plasmid pCAO that has been cut by *Hind* III,

whose digestion generates a sticky ends (See Materials and methods, left column, page 844, Neumann et al., 1982).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Yant et al. regarding somatic integration and long-term transgene expression in mouse hepatocyte using a plasmid DNA comprising Tn5 transposon system, with the teachings of Neumann et al. regarding linearized plasmid DNA that can transfect several folds better than circular DNA to obtain stable transformed mouse cells, to arrive at the claimed invention recited in claims 1, 3, 5, 7, 8, 10, and 12 with a reasonable expectation of success.

One having ordinary skill in the art would have been motivated to combine the teachings of Yant et al. with the teachings of Neumann et al. because Neumann et al. clearly demonstrated higher stable transfection efficiency by linearized DNA molecules as compared to circular/supercoiled DNA molecules.

There would have been a reasonable expectation of success given (1) the successful demonstration of somatic integration and long-term transgene expression in mouse hepatocyte using a plasmid DNA comprising Tn5 transposon system by the teachings of Yant et al., 2000, (2) the characterization of lineralized plasmid DNA molecules work several folds better than circular/supercoiled DNA molecules to obtain stable transformed mouse cells by the teachings of Neumann et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

3. Claims 2, 4, 6, 9, 11, and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Yant et al.** (Yant et al., Somatic integration and long-term transgene expression in normal and haemophilic mice using a DNA transposon system, *Nat Genet.* 25(1):35-41, 2000) in view of **Neumann et al.** (Neumann et al., Gene transfer into mouse lyoma cells by electroporation in high electric fields, *EMBO J.* 1(7):841-5, 1982) as applied to claims 1, 3, 5, 7, 8, 10, and 12 above, and further in view of **Costa et al.** (Costa et al., Site-directed mutagenesis using a rapid PCR-based method, *Methods Mol Biol.* 57:239-48, 1996) and **Promega catalog** (1997) (Promega catalogue, Biological Research Products, 1997, pages 417-426).

The teachings of Yant et al. and Neumann et al. have been discussed in the preceding section of the rejection of claims 1, 3, 5, 7, 8, 10, and 12 under 35 U.S.C. 103(a) as being unpatentable over Yant et al. (2000) in view of Neumann et al. (1982).

However, neither Yant et al. nor Neumann et al. teaches (i) using polymerase chain reaction (PCR) to generate DNA, and (ii) using restriction enzymes whose digestions of DNA generate blunt ends.

Costa et al. (1996) teaches using a PCR-based method to amplify a desired DNA molecule and to perform site-directed mutagenesis for introduction of mutations in a DNA molecule, which involves design of primer sequences; for instance, introduction of a restriction enzyme sites for cloning of PCR amplified DNA molecules (See abstract and Figure 3, Costa et al., 1996) .

Promega catalog (1997) teaches various restriction enzymes and the conditions for the DNA digestion that can generate either stick ends or blunt ends.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to incorporate the teachings by Costa et al. (1996) and Promega catalog (1997) regarding amplification of DNA molecules by PCR and restriction enzyme digestion of DNA, into the combined teachings of Yant et al. and Neumann et al. regarding integration and long-term transgene expression in mouse hepatocyte using a linearized plasmid DNA comprising Tn5 transposon system, to arrive at the claimed invention recited in claims 2, 4, 6, 9, 11, and 13 with a reasonable expectation of success.

One having ordinary skill in the art would have been motivated to incorporate the teachings by Costa et al. and Promega catalog (1997) into the combined teachings of Yant et al. (2000) and Neumann et al. (1982) because (i) Costa et al. (1996) teaches the benefits of PCR to amplify a given DNA molecule and to engineer mutations in the DNA molecule to be cloned in a vector, and (ii) Promega catalog (1997) teaches the flexibility of various restriction enzymes for digestion of DNA for cloning a DNA fragment into a vector.

There would have been a reasonable expectation of success given (1) the successful demonstration of integration and long-term transgene expression in mouse hepatocyte using a linearized plasmid DNA comprising Tn5 transposon system by the combined teachings of Yant et al. (2000) and Neumann et al. (1982), (2) the successful demonstration of using PCR based method for introduction of mutations into a DNA molecule by the teachings of Costa et al. (1996) and the flexibility of various restriction enzymes for digestion of DNA for cloning a DNA fragment into a vector by the teachings of Promega catalog (1997).

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

4. Claims 2, 4, 6, 9, 11, and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Yant et al.** (Yant et al., Somatic integration and long-term transgene expression in normal and haemophilic mice using a DNA transposon system, *Nat Genet.* 25(1):35-41, 2000) in view of **Neumann et al.** (Neumann et al., Gene transfer into mouse lyoma cells by electroporation in high electric fields, *EMBO J.* 1(7):841-5, 1982) as applied to claims 1, 3, 5, 7, 8, 10, and 12 above, and further in view of **Monahan et al.** (US patent 6,379,966 issue date 04/30/2002, filed on 11/29/1999), and **Goldstein et al.** (US patent 5,962,427, issue date 10/05/1999).

The teachings of Yant et al. and Neumann et al. have been discussed in the preceding section of the rejection of claims 1, 3, 5, 7, 8, 10, and 12 under 35 U.S.C. 103(a) as being unpatentable over Yant et al. (2000) in view of Neumann et al. (1982).

However, neither Yant et al. nor Neumann et al. teaches intravascular or interstitial administration as recited in claims 14, 15, and 17.

Regarding the limitation "delivered to cells intravascularly" recited in claim 14 and the limitation "delivered intravascularly using pressure" recited in claim 15, Monahan et al. (2002) teaches intravascular delivery of non-viral nucleic acid and the efficiency of polynucleotide delivery and expression of non-viral nucleic acid is increased by the intravascular hydrostatic (physical) pressure (See bridging paragraph, column 2-3, Monahan et al., 2002).

Regarding the limitation "delivered by direct interstitial injection" recited in claim 17, Goldstein et al. (1999) teaches administration of DNA associated with liposomes formulated in liquid carrier solutions for injection into interstitial spaces for *in vivo* plasmid DNA transfer into cells (See lines 4-10, column 4, section 2.2 Gene therapy, Goldstein et al. 1999)

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to incorporate the teachings by Monahan et al. (2002) and Goldstein et al. (1999) regarding various routes of administration of non-viral plasmid, into the combined teachings of Yant et al. and Neumann et al. regarding integration and long-term transgene expression in mouse hepatocyte using a linearized plasmid DNA comprising Tn5 transposon system, to arrive at the claimed invention recited in claims 14, 15, and 17 with a reasonable expectation of success.

One having ordinary skill in the art would have been motivated to incorporate the teachings by Monahan et al. (2002) and Goldstein et al. (1999) into the combined teachings of Yant et al. (2000) and Neumann et al. (1982) because (i) Monahan et al. (2002) teaches that the delivery and expression of non-viral nucleic acid and is increased by the intravascular hydrostatic (physical) pressure, and (ii) Goldstein et al. (1999) teaches that DNA trapped in liposomes can be directly transferred to cells *in vivo* by injection into interstitial spaces. The combined teachings of Monahan et al. (2002) and Goldstein et al. (1999) show various administration routes to facilitate gene therapy to target DNA into desired cells of a given tissue, including hepatocyte of liver tissue taught by Yant et al. (2000).

There would have been a reasonable expectation of success given (1) the successful demonstration of integration and long-term transgene expression in mouse hepatocyte using a linearized plasmid DNA comprising Tn5 transposon system by the combined teachings of Yant et al. (2000) and Neumann et al. (1982), (2) the successful demonstration of increased delivery and expression of non-viral nucleic acid by the intravascular hydrostatic (physical) pressure by

the teachings of Monahan et al. (2002), and effective transfer of DNA trapped in liposomes to cells *in vivo* by injection into interstitial spaces by the teachings of Goldstein et al. (1999).

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Conclusion

5. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Wu-Cheng Winston Shen/, Ph. D.
Patent Examiner
Art Unit 1632